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ORIGINAL RESEARCH

Second Primary Malignancy in Patients with Hypopharyngeal Carcinoma: A SEER-Based Study

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Background: A population-based analysis of the risk of secondary primary malignancy (SPM) in patients with hypopharyngeal carcinoma (HPC) has been lacking in the literature. Therefore, we conducted this study to determine the risk factors and assess the effects of SPM on the overall survival (OS) and cancer-specific survival (CSS) of patients with HPC.

Methods: Data on selected patients diagnosed with HPC from the Surveillance, Epidemiology and End Results (SEER) database between 1973 and 2015 were examined through logistic regression, Cox regression and nomogram methods.

Results: The overall risk of SPM in patients with HPC was higher than that in the general population (SIR: 2.77; $P < 0.05$). The specific-site, including the oral cavity, pharynx, digestive system, respiratory system and endocrine system, had a relatively higher risk of SPM. The overall risks of the subgroup of people 55–75 years of age and all subgroups of sex, race and latency were significantly elevated. In addition, patients with HPC were more likely to have been diagnosed in 2010–2015 (vs 2004–2009; $P = 0.002$), to be unmarried (vs married; $P = 0.008$), to have distant metastasis (vs no metastasis; $P = 0.016$) and to have had no surgery for the first tumor (vs surgery for the first tumor; $P = 0.021$), and these aspects were associated with a significantly elevated risk of developing SPM. SPM was independently associated with better OS and CSS. The OS and CSS in patients with HPC with SPM were better than those in patients without SPM (log rank $P < 0.0001$). The C indexes of the nomogram constructed with ten influencing factors including SPM were 0.681:0.699 for OS and 0.705:0.724 for CSS (training cohort:validation cohort).

Conclusion: Although the overall risk of SPM in patients with HPC was elevated, SPM did not decrease the OS and CSS in patients with HPC. This finding is inconsistent with clinical observations and thus requires further research and exploration. It possibly because HPC might have a shorter survival time, or the follow-up time was not long enough.

Keywords: hypopharyngeal carcinoma, HPC, secondary primary malignancy, SPM, SEER, nomogram

Introduction

Hypopharyngeal carcinoma (HPC) is the most aggressive subtype of head and neck cancer. Over recent decades, the incidence of HPC has increased each year.[1] In addition, the prognosis of HPC is often poor, because its hidden anatomical location hinders detection.[2] Currently, HPC treatment remains based on surgical resection, supplemented by adjuvant chemotherapy and radiotherapy.[3,4] With the continual improvements in diagnostic technology and therapy methods, the survival rates of patients with HPC have also increased. However, with this increased survival time, multiple complications have begun to be observed.[5]

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Table 1 Site-Specific Risk of SPM in Patients with HPC

Site of Second Primary Malignancy	Observed	Expected	SIR	95% CI
All Sites	1275	460.45	2.77#	2.62—2.93
All Solid Tumors	1220	412.28	2.96#	2.80—3.13
Oral cavity and pharynx	233	12.69	18.37#	16.08—20.88
Tongue	82	2.93	27.99#	22.26–34.74
Floor of Mouth	23	1.09	21.07#	13.36–31.62
Nasopharynx	7	0.50	14.10#	5.67–29.05
Esophagus	146	6.21	23.53#	19.87–27.67
Digestive System	304	95.01	3.20#	2.85—3.58
Respiratory System	479	82.89	5.78#	5.27—6.32
Bones and Joints	0	0.38	0	0—9.75
Soft Tissue including Heart	5	1.97	2.54	0.83—5.93
Skin excluding Basal and Squamous	9	14.85	0.61	0.28—1.15
Breast	18	23.59	0.76	0.45—1.21
Female Genital System	6	9.72	0.62	0.23—1.34
Male Genital System	105	120.31	0.87	0.71—1.06
Urinary System	51	42.20	1.21	0.90—1.59
Eye and Orbit	2	0.65	3.08	0.37—11.11
Brain and Other Nervous System	3	4.49	0.67	0.14—1.95
Endocrine System	8	3.08	2.60#	1.12—5.12
Adrenal Gland	3	0.13	22.64#	4.67–66.18
Thyroid	5	2.71	1.84	0.60–4.29
All Lymphatic and Hematopoietic Diseases	29	36.23	0.80	0.54—1.15
Mesothelioma	0	1.45	0	0—2.54
Kaposi Sarcoma	0	0.44	0	0—8.30
Miscellaneous	23	10.51	2.19#	1.39—3.29

Note: #P<0.05.

Table 2 Age at Diagnosis, Sex, Race and Latency Impact on the Overall Risk of Developing SPM in Patients with HPC

Parameters	Observed	Expected	SIR	95% CI
Age at diagnosis, years				
≤55	275	59.98	4.58	0.89–10.93
55–75	896	338.23	2.65#	1.68–3.63
≥75	104	62.26	1.67	0.58–2.45
Sex				
Male	1020	379.93	2.68#	2.52–2.85
Female	255	80.52	3.17#	2.79–3.58
Race				
White	1006	380.52	2.64#	2.48—2.81
Black	197	59.71	3.30#	2.85—3.79
Other	72	19.79	3.64#	2.85—4.58
Latency				
2–11 months	165	74.22	2.22#	1.90–2.59
12–59 months	552	173.95	3.17#	2.91–3.45
60–119 months	333	112.34	2.96#	2.65–3.30
≥120 months	225	99.95	2.25#	1.97–2.57

Note: #P<0.05.

Secondary primary malignancy (SPM), a long-term complication of cancer, has received increasing interest in recent years.[6,7] Numerous studies have shown that SPM often occurs after the treatment of various solid tumors.[8,9] Previous studies on SPM have focused mostly on other types of head and neck cancer, but rarely on HPC.[10,11] Smoking, drinking, HPV infection and genetic microenvironmental factors are important influences on the occurrence and development of HPC.[12] However, the risk factors for SPM in patients with HPC are unclear, and the effects of SPM have not been effectively assessed. With the increase in the number of cancer survivors, the risk of SPM in patients must be assessed to provide insights for the further treatment of cancer.[13] Our study clarified the overall and site-specific risks of SPM in patients with HPC, assessed the effects of SPM on overall survival (OS) and cancer-specific survival (CSS), and further constructed and verified a nomogram for predicting the 3-year, 5-year and 10-year OS and CSS. Our study provides new evidence of the effects of clinical treatment of SPM in HPC survival.

The Surveillance, Epidemiology, and End Results (SEER) database, affiliated with the National Cancer Institute, collects and reports cancer survival data from several central cancer registries, which manage approximately 30% of the population in the USA. From the SEER database, we obtained data from a large cohort and conducted a comparative analysis of patients with HPC with vs without SPM, to clarify the effects of SPM on patients with HPC.

Methods

Patient Selection

We used the data set Incidence-SEER 9 Regs Research Data, Nov 2017 Sub (1973–2015) <Katrina/Rita Population Adjustment> to analyze the multiple primary

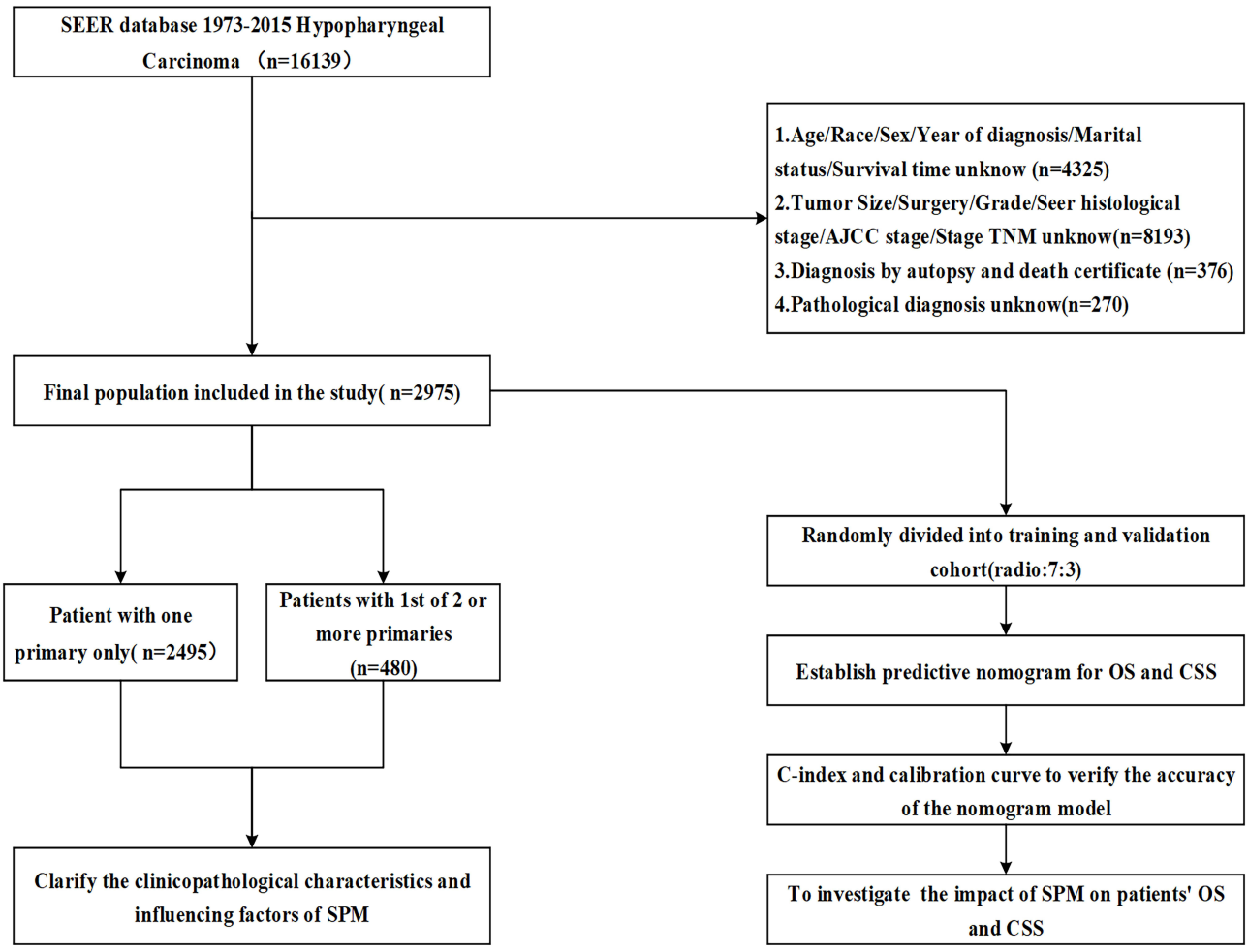

Figure 1 Flowchart of data selection.

Table 3 Clinicopathological Characteristics of Patients with HPC as the Lone Primary and Those with HPC as the First of Two or More Primaries

	One Primary (n = 2495)	First of Two or More Primaries (n = 480)	P-value
Year of diagnosis			0.027
2004–2009	1248 (50.02%)	283 (58.96%)	
2010–2015	1247 (49.98%)	197 (41.04%)	
Age at diagnosis, years			0.140
<55	541 (21.68%)	95 (19.79%)	
55–75	1550 (62.12%)	319 (66.46%)	
≥75	404 (16.19%)	66 (13.75%)	
Sex			0.356
Male	2035(81.56%)	397(82.71%)	
Female	460 (18.44%)	83(17.29%)	
Race			0.257
White	1879 (75.31%)	364(75.83%)	
Black	458 (18.36%)	86(17.92%)	
Other	158 (6.33%)	30(6.25%)	
Marital status			0.075
Married	1147 (45.97%)	259(53.96%)	
Unmarried	1348 (54.03%)	221(46.04%)	
Grade			0.140
Grade I, well differentiated	120 (4.81%)	23(4.79%)	
Grade II, moderately differentiated	1261(50.54%)	259(53.96%)	
Grade III, poorly differentiated	1067(42.77%)	193(40.21%)	
Grade IV, undifferentiated	47(1.88%)	5(1.04%)	
SEER histological stage			0.137
Localized	200(8.02%)	51(10.63%)	
Regional	1393(55.83%)	293(61.04%)	
Distant	902(36.15%)	136(28.33%)	
AJCC sixth stage			0.212
I	76(3.05%)	19(3.96%)	
II	247(9.90%)	76(15.83%)	
III	436(17.47%)	93(19.38%)	
IV	1736(69.58%)	292(60.83%)	
Stage T			0.035
T1	230(9.22%)	46(9.58%)	
T2	862(34.55%)	211(43.96%)	
T3	470(18.84%)	86(17.92%)	
T4	933(37.39%)	137(28.54%)	
Stage N			0.062
N0	659(26.41%)	159(33.13%)	
N1	538(21.56%)	98(20.42%)	
N2	1162(46.57%)	204(42.5%)	
N3	136(5.45%)	19(3.96%)	
Stage M			0.436
M0	2292(91.86%)	462(96.25%)	
M1	203(8.14%)	18(3.75%)	

(*Continued*)

Table 3 (Continued).

	One Primary (n = 2495)	First of Two or More Primaries (n = 480)	P-value
Tumor size			0.251
<2cm	1824(73.11%)	358(74.58%)	
2–5cm	44(1.76%)	6(1.25%)	
>5cm	627(25.13%)	116(24.17%)	
Surgery for first primary site			0.348
Yes	526(21.08%)	131(27.29%)	
No	1969(78.92%)	349(72.71%)	
Number of primaries			-
2 Primaries	-	432(90%)	
3 Primaries	-	40(8.33%)	
4 Primaries	-	7(1.46%)	
5 Primaries	-	0(-)	
6 Primaries	-	1(0.21%)	

standardized incidence ratio. The data set Incidence – SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (1973–2015 varying) was used for case selection. Patients were selected according to the following inclusion criteria: (1) diagnosis confirmed by positive histology; (2) diagnosis of HPC by histopathology; (3) SPM of HPC, indicating that HPC was the first cancer of two or more primary malignancies; (4) availability of complete information for all selected patient variables.

Definition

With reference to the definition of multiple primary malignancy in the SEER database, the criteria used in our study were as follows: (1) ICD-O-3 histology codes indicating that the first three different tumors were multiple primary malignancies; (2) an invasive tumor diagnosed more than 60 days after the in situ tumor diagnosis, indicating multiple primary malignancies. Latency was defined as the time interval from the diagnosis of HPC to the diagnosis of SPM. The standardized incidence ratio (SIR), an indicator of SPM risk, was calculated by dividing the number of observed SPM cases by the expected number in the general population.

Statistical Analyses

We used SEER*Stat version 8.3.6 (http://seer.cancer.gov/seerstat/) to retrieve data from the SEER database. A two-way analysis of variance (ANOVA) was used to compare the means for continuous variables, whereas a chi-squared test was used for categorical variables. Multivariable logistic regression was used to clarify the effects of individual factors on the presence of SPM. Survival estimates were obtained with the Kaplan–Meier method. Multivariable Cox regression was used to analyze the independent factors influencing OS and CSS in patients with HPC. A P-value <0.05 was considered statistically significant. SPSS (release 22.0, IBM Corporation, Armonk, NY, USA) was used for statistical analysis, and R version 4.0.4 (R Foundation) was used for nomograms.

Results

Risk of SPM at Different Anatomical Sites, According to Age, Sex, Race and Latency

According to our statistical results (Table 1), the overall risk of SPM in patients with HPC was significantly higher than that in the general population (SIR: 2.77; 95% CI: 2.62–2.93; P < 0.05). The risk of SPM was significantly elevated in certain areas, including all solid tumors, the oral cavity, pharynx, digestive system, respiratory system, endocrine system and other areas, particularly the tongue, floor of the mouth, nasopharynx, esophagus and adrenal glands. The risk of SPM at other anatomical sites in patients with HPC did not change significantly.

Diagnosis age, sex, race and latency may be factors affecting the SIR of SPM. Therefore, we further evaluated the effects of these factors on the risk of SPM in patients with HPC. As shown in Table 2, in patients 55–75 years of

Table 4 Multivariable Logistic Regression for the Presence of SPM After HPC Diagnosis

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Year of diagnosis				
2004–2009	1[Reference]		1[Reference]	
2010–2015	1.435(1.177–1.750)	<0.001	1.389(1.128–1.711)	0.002
Age at diagnosis, years				
<55	1[Reference]			
55–75	0.835(0.665–1.095)	0.212	-	-
≥75	1.075(0.765–1.509)	0.677	-	-
Sex				
Female	1[Reference]			
Male	0.925(0.715–1.196)	0.552	-	-
Race				
White	1[Reference]			
Black	1.032(0.798–1.333)	0.811	-	-
Other	1.020(0.680–1.531)	0.923	-	-
Marital status				
Married	1[Reference]		1[Reference]	
Unmarried	1.377(1.132–1.676)	<0.001	1.308(1.072–1.595)	0.008
Grade				
Grade I, well differentiated	1[Reference]			
Grade II, moderately differentiated	0.933(0.586–1.487)	0.771	-	-
Grade III, poorly differentiated	1.060(0.661–1.698)	0.810	-	-
Grade IV, undifferentiated	1.802(0.647–5.018)	0.260	-	-
SEER histological stage				
Localized	1[Reference]			
Regional	1.212(0.870–1.690)	0.256	-	-
Distant	1.691(1.184–2.415)	0.004	-	-
AJCC sixth stage				
I	1[Reference]			
II	0.813(0.462–1.429)	0.471	-	-
III	1.172(0.676–2.032)	0.572	-	-
IV	1.486(0.886–2.494)	0.134	-	-
Stage T				
T1	1[Reference]			
T2	0.817(0.575–1.160)	0.259	-	-
T3	1.093(0.739–1.616)	0.656	-	-
T4	1.362(0.947–1.960)	0.096	-	-
Stage N				
N0	1[Reference]			
N1	1.325(1.005–1.746)	0.046	-	-
N2	1.374(1.094–1.727)	0.006	-	-
N3	1.727(1.037–2.877)	0.036	-	-
Stage M				
M0	1[Reference]		1[Reference]	
M1	2.273(1.390–3.719)	<0.001	1.911(1.130–3.234)	0.016

(*Continued*)

Table 4 (Continued).

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Tumor size				
<2cm	1[Reference]			
2–5cm	1.439(0.609–3.403)	0.407	-	-
>5cm	1.061(0.844–1.333)	0.612	-	-
Surgery for first primary site				
Yes	1[Reference]		1[Reference]	
No	1.405(1.125–1.756)	0.003	1.305(1.041–1.637)	0.021

age, the overall risk of SPM increased by 2.65-fold. After stratification by sex, the risks among men and women increased by 2.68 fold and 3.17 fold, respectively. Among race groups, the risks of white, black and other races increased by 2.64 fold, 3.30 fold and 3.64 fold, respectively. Analysis according to the latency group indicated that the risks of 2–11 months, 12–59 months, 60–119 months and ≥120 months increased by 2.22 fold, 3.17 fold, 2.96 fold and 2.25 fold, respectively.

Characteristics of Patients with and without SPM

The process of selecting patients is shown in Figure 1. From the SEER database, we selected 2975 patients with HPC, of whom 2495 had only one primary tumor, and the other 480 had HPC as the first tumor among two or more primary malignancies. Table 3 summarizes the clinicopathological characteristics of patients with HPC as the only primary malignancy and those with HPC as the first tumor among two or more primary malignancies. Among patients with HPC with SPM, 90% had two primary tumors, and 10% had at least three primary tumors. According to statistical results, patients with SPM vs without SPM showed a significant difference in year of diagnosis and stage T. However, no significant differences were observed between groups in terms of age, race, sex, marital status, tumor grade, SEER histological stage, American Joint Committee on Cancer (AJCC) sixth stage, stage N, stage M, tumor size and the primary site of surgery.

Risk Factors for SPM

We used multivariate logistic regression to clarify the risk factors for SPM in patients with HPC. As shown in

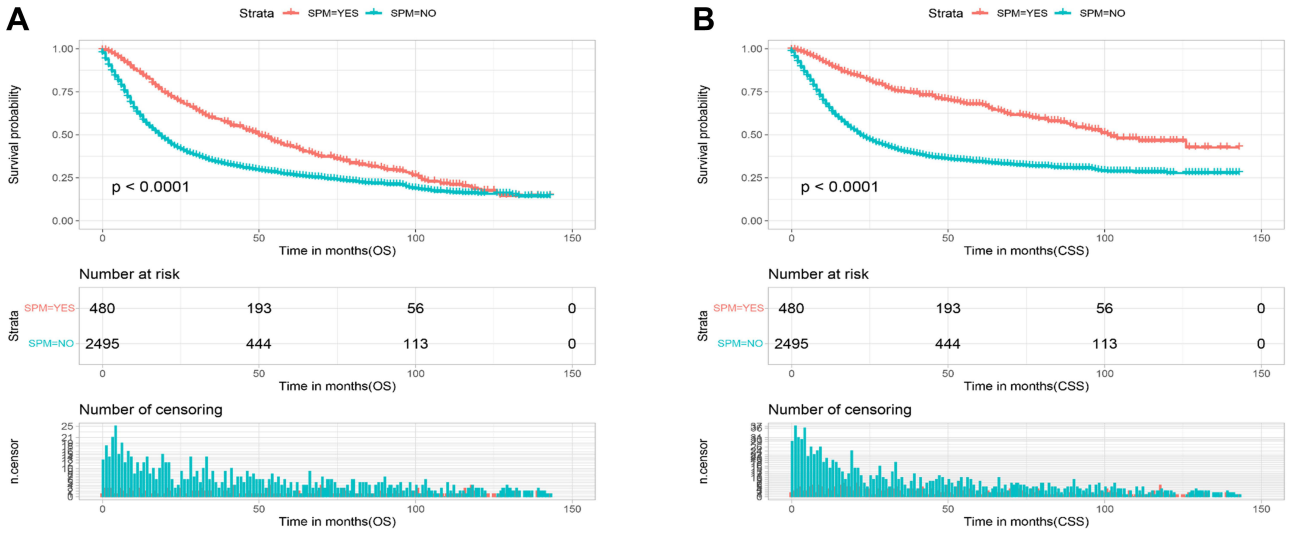

Figure 2 OS and CSS in patients with HPC with or without SPM. (**A**) OS in patients with HPC with or without SPM (**B**) CSS in patients with HPC with or without SPM.

Table 5 Multivariable Cox Regression for OS and CSS in Patients with HPC

	Multivariate Analysis (OS)		Multivariate Analysis (CSS)	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Year of diagnosis				
2004–2009	1[Reference]		1[Reference]	
2010–2015	0.882(0.799–0.973)	0.012	0.834(0.747–0.934)	0.001
Age at diagnosis, years				
<55	1[Reference]		1[Reference]	
55–75	1.237(1.103–1.387)	<0.001	1.194(1.050–1.358)	0.007
≥75	2.161(1.865–2.503)	<0.001	1.993(1.686–2.356)	<0.001
Sex				
Female	1[Reference]		1[Reference]	
Male	1.077(0.958–1.211)	-	1.068(0.935–1.221)	-
Race				
White	1[Reference]		1[Reference]	
Black	1.368(1.223–1.530)	<0.001	1.343(1.183–1.525)	<0.001
Other	0.887(0.734–1.072)	-	0.941(0.762–1.163)	-
Marital status				
Married	1[Reference]		1[Reference]	
Unmarried	1.402(1.279–1.538)	<0.001	1.396(1.256–1.551)	<0.001
Grade				
Grade I, well differentiated	1[Reference]		1[Reference]	
Grade II, moderately differentiated	0.976(0.789–1.208)	-	0.961(0.755–1.224)	-
Grade III, poorly differentiated	0.882(0.711–1.094)	-	0.886(0.694–1.131)	-
Grade IV, undifferentiated	0.856(0.573–1.278)	-	0.940(0.608–1.453)	-
SEER histological stage				
Localized	1[Reference]		1[Reference]	
Regional	1.063(0.811–1.394)	-	1.037(0.739–1.455)	-
Distant	1.066(0.795–1.428)	-	1.061(0.740–1.523)	-
AJCC sixth stage				
I	1[Reference]		1[Reference]	
II	0.969(0.617–1.521)	-	1.437(0.769–2.685)	-
III	1.024(0.628–1.669)	-	1.573(0.810–3.056)	-
IV	1.098(0.673–1.792)	-	1.859(0.956–3.614)	-
Stage T				
T1	1[Reference]		1[Reference]	
T2	1.477(1.176–1.855)	<0.001	1.481(1.134–1.935)	0.004
T3	1.645(1.296–2.0582)	<0.001	1.739(1.322–2.287)	<0.001
T4	2.158(1.712–2.719)	<0.001	2.313(1.768–3.026)	<0.001
Stage N				
N0	1[Reference]		1[Reference]	-
N1	1.137(0.962–1.343)	-	1.151(0.953–1.389)	-
N2	1.154(0.990–1.344)	-	1.204(1.016–1.429)	0.032
N3	1.544(1.228–1.941)	<0.001	1.624(1.263–2.088)	<0.001
Stage M				
M0	1[Reference]		1[Reference]	
M1	2.335(1.970–2.769)	<0.001	2.286(1.901–2.749)	<0.001

(*Continued*)

Table 5 (Continued).

	Multivariate Analysis (OS)		Multivariate Analysis (CSS)	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Tumor size				
<2cm	1[Reference]		1[Reference]	
2–5cm	0.982(0.649–1.485)	-	0.983(0.602–1.604)	-
>5cm	1.186(1.070–1.314)	<0.01	1.261(1.124–1.415)	<0.001
Surgery for first primary site				
Yes	1[Reference]		1[Reference]	
No	1.286(1.146–1.442)	<0.001	1.314(1.150–1.502)	<0.001
Number of primaries				
Multiple primary	1[Reference]		1[Reference]	
One Primary	1.575(1.391–1.783)	<0.001	2.435(2.058–2.881)	<0.001

Table 4, a year of diagnosis of 2010–2015 (vs 2004–2009; HR: 1.389; 95% CI: 1.128–1.711; P = 0.002), being unmarried (vs married; HR: 1.308; 95% CI: 1.072–1.595; P = 0.008), having distant metastasis (vs no metastasis; HR: 1.911; 95% CI: 1.130–3.234; P = 0.016) and not having undergone surgery for the first primary tumor (vs having undergone surgery; HR: 1.305; 95% CI: 1.041–1.637; P = 0.021) were associated with a significantly greater risk of SPM. Factors including age, race, sex, tumor grade, SEER histological stage, AJCC sixth stage, stage T, stage N and tumor size were not significantly associated with the development of SPM.

The Effects of SPM on Prognosis

After clarifying the incidence of SPM and the site-specific risk of SPM, we next explored the effects of SPM on the prognosis of patients with HPC. The OS of patients with SPM was better than that of patients without SPM (log-rank = 63.509, P < 0.0001) (Figure 2A). The median OS and the corresponding 95% CI of patients with SPM and without SPM were 50 (43.163–56.837) months and 19 (17.638–20.362) months, respectively. The CSS of patients with SPM was better than that of patients without SPM (log rank = 133.233, P < 0.0001) (Figure 2B). The median CSS and the corresponding 95% CI were 102 (81.769–122.231) months and 22 (20.022–23.978) months, respectively.

We further used multivariate Cox regression analysis to identify variables that might affect the OS and CSS of patients with HPC. As shown in Table 5, the absence of SPM was an independent factor associated with poorer OS (HR: 1.575; 95% CI: 1.391–1.783; P < 0.001). Variables significantly associated with decreased OS were a year of diagnosis of 2004–2009, age 55–75 years, age ≥75 years, black race, unmarried status, stage T2, T3, T4, stage N3, stage M1, tumor size >5 cm and no surgery for the first tumor. In addition, as shown in Table 5, the absence of SPM was an independent factor associated with poorer CSS (HR: 2.435; 95% CI: 2.058–2.881; P < 0.001). Variables significantly associated with decreased CSS were a year of diagnosis of 2004–2009, age 55–75 years and age ≥75 years, black race, unmarried status, stage T2, T3, T4, stage N2, N3, stage M1, tumor size >5 cm and no surgery for the first tumor.

Nomogram for OS and CSS

We divided all included patients into a training cohort and validation cohort randomly in a ratio of 7:3. According to the statistical results in Table 6, patients in the training cohort vs patients in the validation cohort showed a significant difference in the year of diagnosis, marital status and stage T. Figure 3A shows the prognostic nomogram of all important independent predictors of OS in the training cohort of patients with HPC. The prediction C-index for OS was 0.681 and 0.699 in the training cohort and validation cohort, respectively. As shown in Figure 4, the calibration plots for the survival probabilities of patients in the training cohort and validation cohort at 3, 5 and 10 years were in agreement. Figure 3B shows the prognostic nomogram of important independent predictors of CSS in the training cohort of patients with HPC. The prediction C-index for CSS was 0.705 and 0.724 in the training

Table 6 Clinicopathological Characteristics of Patients in Training Cohort and Validation Cohort

	Training Cohort (n = 2084)	Validation Cohort Primaries (n = 891)	P-value
Year of diagnosis			0.014
2004–2009	1057(50.72%)	474(53.20%)	
2010–2015	1027(49.28%)	417(46.80%)	
Age at diagnosis, years			0.160
<55	445(21.35%)	191(21.43%)	
55–75	1314(63.05%)	555(62.29%)	
≥75	325(15.60%)	145(16.27%)	
Sex			0.334
Male	1687(80.95%)	745(83.61%)	
Female	397(19.05%)	146(16.39%)	
Race			0.269
White	1579(75.77%)	664(74.52%)	
Black	379(18.19%)	165(18.52%)	
Other	126(6.05%)	62(6.96%)	
Marital status			0.041
Married	982(47.12%)	424(47.59%)	
Unmarried	1102(52.88%)	467(52.41%)	
Grade			0.148
Grade I, well differentiated	95(4.56%)	48(5.39%)	
Grade II, moderately differentiated	1065(51.10%)	455(51.07%)	
Grade III, poorly differentiated	888(42.61%)	372(41.75%)	
Grade IV, undifferentiated	36(1.73%)	16(1.80%)	
SEER histological stage			0.148
Localized	167(8.01%)	84(9.43%)	
Regional	1182(56.72%)	504(56.57%)	
Distant	735(35.27%)	303(34.01%)	
AJCC sixth stage			0.188
I	64(3.07%)	31(3.48%)	
II	220(10.56%)	103(11.56%)	
III	381(18.28%)	148(16.61%)	
IV	1419(68.09%)	609(68.35%)	
Stage T			0.035
T1	194(9.31%)	82(9.20%)	
T2	748(35.89%)	325(36.48%)	
T3	385(18.47%)	171(19.19%)	
T4	757(36.32%)	313(35.13%)	
Stage N			0.060
N0	567(27.21%)	251(28.17%)	
N1	446(21.40%)	190(21.32%)	
N2	961(46.11%)	405(45.45%)	
N3	110(5.28%)	45(5.05%)	
Stage M			0.456
M0	1935(92.85%)	819(91.92%)	
M1	149(7.15%)	72(8.08%)	

(*Continued*)

Table 6 (Continued).

	Training Cohort (n = 2084)	Validation Cohort Primaries (n = 891)	P-value
Tumor size			0.237
<2cm	1513(72.60%)	669(75.08%)	
2–5cm	41(1.97%)	9(1.01%)	
>5cm	530(25.43%)	213(23.91%)	
Surgery for first primary site			0.355
Yes	441(21.16%)	216(24.24%)	
No	1643(78.84%)	675(75.76%)	
Number of primaries			0.379
First of 2 or more Primaries	336(16.12%)	144(16.16%)	
One Primary	1748(83.88%)	747(83.83%)	

cohort and validation cohort, respectively. As shown in Figure 5, the calibration plots for the survival probabilities of patients in the training cohort and validation cohort at 3, 5 and 10 years were in agreement.

Discussion

In recent years, the number of cancer survivors has increased with advances in diagnosis and treatment technologies; consequently, various long-term cancer complications have attracted increasing attention.[14,15] As the survival time of cancer patients is prolonged, SPM, a long-term complication, is appearing increasingly frequently.[16–18] Exploring the prevalence and risk factors for SPM would aid in preventing the occurrence of SPM and in further improving the quality of life of cancer survivors.

With the rapid development of precision medicine, formulating personalized diagnosis and treatment strategies becomes increasingly necessary. Nomograms can integrate statistics and clinicopathological characteristics to predict the effects of various factors on the survival time for patients with malignant tumors.[19–21] This study included ten independent influencing factors including SPM to establish an HPC OS and CSS nomogram, and further used the C index and calibration curve to verify its better predictability. In previous studies, Ali et al and Shen et al have constructed nomograms to predict the survival of patients with head and neck squamous cell carcinoma and basaloid squamous cell carcinoma, which had not been widely used for HPC because of the wide range of research.[22,23] Then, Lin et al, Tang, Gong et al and Tian et al constructed nomograms for predicting survival in patients with hypopharyngeal squamous-cell carcinoma.[12,24,25] However, SPM was not included in their nomograms. Our study is the first study of SPM in patients with HPC. We verified the better performance of the C index of our nomogram (0.681:0.699 for OS and 0.705:0.724 for CSS, training cohort: validation cohort), thus enabling theoretical insights based on large data sets for the clinical treatment of SPM.

Our study showed that the overall risk of SPM in patients with HPC was higher than that in the general population. Notably, the site-specific risk of SPM in the oral cavity, pharynx, digestive system and respiratory system was significantly elevated. Patients 55–75 years of age had an elevated risk of SPM, and the incidence of SPM in all subgroups of sex, race and latency was higher than that in the general population. Given this result, we recommend that patients 55–75 years of age with HPC undergo regular respiratory and digestive endoscopy examinations. Possible reasons for the high rates of SPM in the oral cavity and pharynx are as follows: First, the anatomical locations of the oral cavity, oropharynx, nasopharynx and hypopharynx are in proximity. Second, smoking, drinking and HPV infection are common risk factors for HPC, oral cancer and oropharyngeal cancer.[26–28] Finally, HPC and oral cancer may be associated with mutations in similar oncogenes.[29,30]

In our study, the respiratory system and digestive system were found to be relatively prone to malignant tumors after HPC, possibly because of their proximate anatomical locations. Moreover, the risk of adrenal tumors in survivors of HPC was also significantly elevated. Previous studies based on the SEER database have shown that adrenal tumors are likely to occur not only after HPC, but also after other endocrine tissue tumors, gastrointestinal tumors and hepatic carcinomas.[31] In addition,

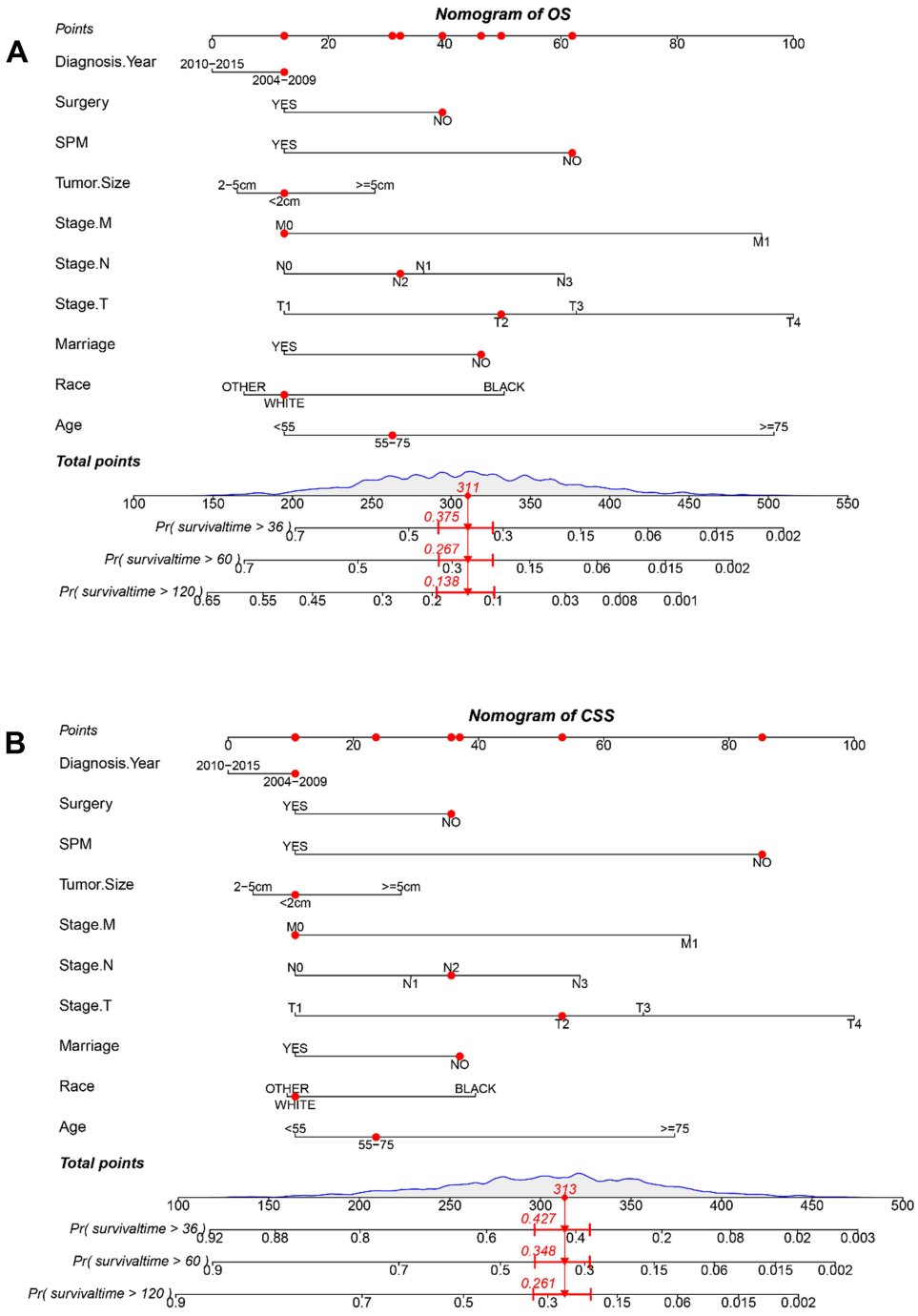

Figure 3 OS nomogram and CSS nomogram in patients with HPC. (**A**) OS nomogram. (**B**) CSS nomogram.

previous studies have shown that survivors of Hodgkin's lymphoma, hepatic carcinoma, stomach cancer, kidney cancer and prostate cancer have an increased risk of thyroid cancer.[32–36] However, our analysis showed that the risk of developing thyroid cancer after HPC did not increase significantly. SEER-based studies have shown that cancer survivors are more likely to develop endocrine system tumors (eg, in the thyroid and adrenal glands). The cause may be associated with changes in hormone levels after the occurrence of the first cancers; however, the specific underlying reasons remain unclear.

Our study also showed that a year of diagnosis of 2010–2015, being unmarried, having stage M1 tumors and not undergoing surgery for the primary tumor were associated with greater risk of SPM. A year of diagnosis of 2010–2015 was more associated with the development of

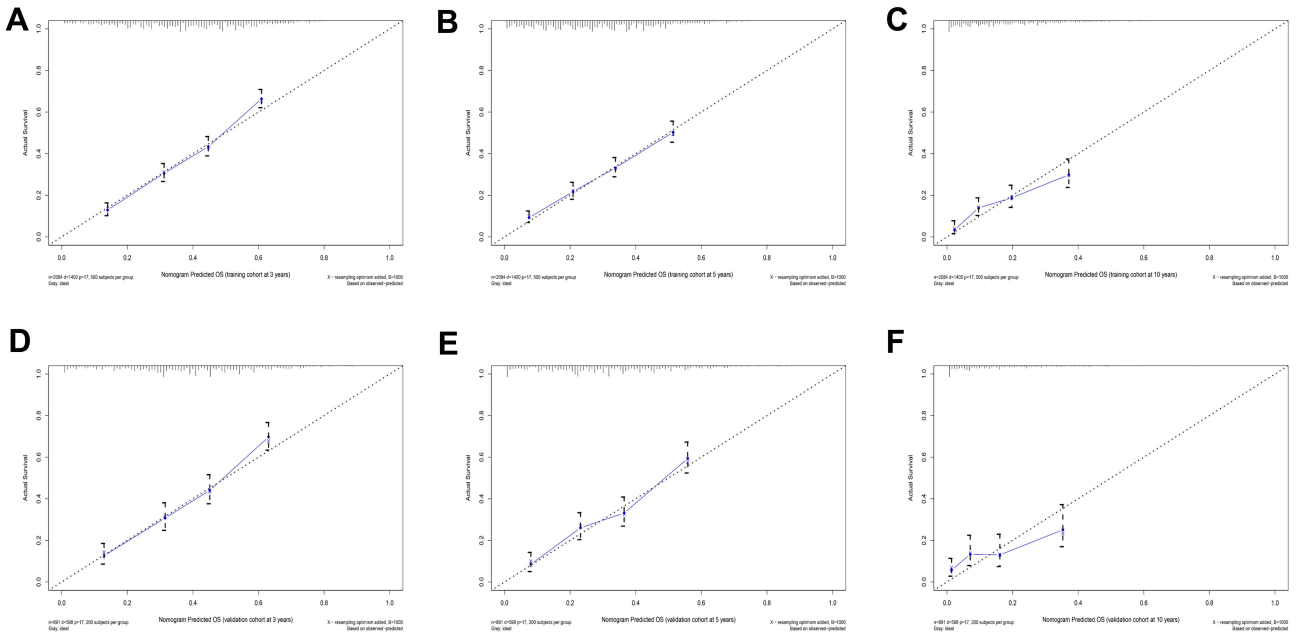

Figure 4 Calibration curve for predicting patient OS at 3, 5, and 10 years. (**A**–**C**) Calibration curve for training cohort OS at 3,5,10 years. (**D**–**F**) Calibration curve for validation cohort OS at 3,5,10 years.

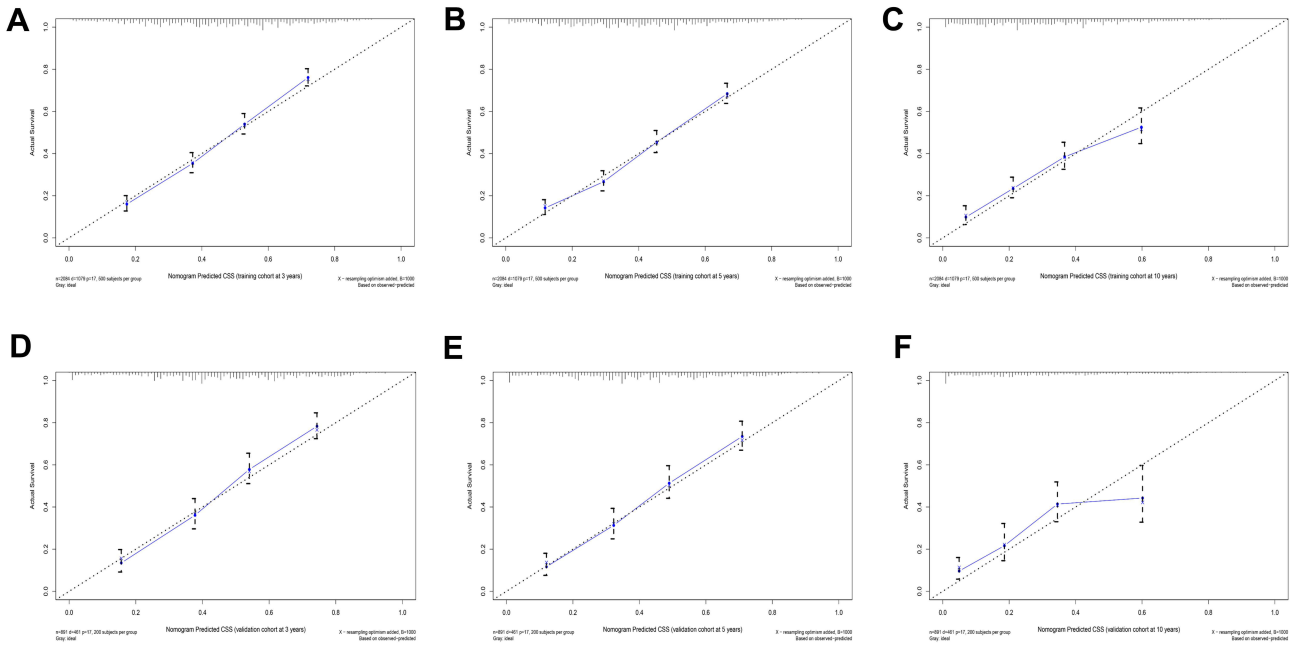

Figure 5 Calibration curve for predicting patient CSS at 3, 5, and 10 years. (**A**–**C**) Calibration curve for training cohort CSS at 3, 5, 10 years. (**D**–**F**) Calibration curve for validation cohort CSS at 3, 5, 10 years.

SPM than a year of diagnosis of 2004–2009. This finding may be because with the development of medical technology enabled better diagnosis and follow-up of SPM in 2010–2015. Having undergone surgery for HPC was an unfavorable factor in the development of SPM. For patients with early stage HPC, surgery is currently the best treatment.[37] Our results further verify the necessity of surgery for patients with HPC.

Furthermore, we found that SPM was an independent factor associated with the OS and CSS of patients with HPC, and patients with SPM had a better OS and CSS than patients without SPM. In previous studies, patients

with cholangiocarcinoma with SPM have also been observed to have a better OS and CSS than those without SPM.[36] Patients with cervical cancer with SPM have been found to experience better OS within 6 years than those without SPM.[38] However, this result may be inconsistent with clinical observations. The first possible reason for this discrepancy is that HPC might have a shorter survival time than other types of SPM tumors; the second is that the follow-up time might not have been long enough. However, the reason is not yet clear, and further exploration of clinical cases with more detailed information is needed.

Our study is the first to explore the factors influencing SPM in HPC and the effects of SPM on OS and CSS in patients with HPC. However, several study limitations were inevitable. First, because of the lack of information on patients' living habits and family history, the possibility of evaluating more factors influencing SPM was limited. Second, the number of patients with HPC with complete information for each variable in the plus database containing radiotherapy and chemotherapy was relatively small. In order to make the results more reliable, our study did not include radiotherapy and chemotherapy information. Third, although the SPM that we included was in patients who were more than 2 months after the diagnosis of HPC, the recurrence and metastasis of HPC could not be completely ruled out. However, SPM is strictly defined in the SEER database, which is one of the best cancer registration systems in the worldwide.

Conclusion

We found that patients with HPC have a higher overall risk of SPM than the general population. The specific sites where the risk of SPM was elevated included all solid tumors, particularly the oral cavity, pharynx, digestive system, respiratory system and adrenal glands. The OS and CSS were longer for patients with SPM than without SPM, possibly because HPC might have a shorter survival time, or the follow-up time was not long enough. Therefore, for patients with HPC, especially those aged 55–75 years, digestive system endoscopy, respiratory system endoscopy and adrenal CT should be considered to detect the formation of SPM.

Ethical Statement

The patient information in the SEER database is obtained anonymously and publicly, and the patient's informed consent is not required. Our work was conducted in accordance with the Declaration of Helsinki (2013), and was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University (The Examination and Approval No. Review [2021] No. (009)).

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Author Contributions

All authors contributed to study design, data collection, statistical analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that no conflicts of interest in this work.

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